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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
THOMAS, TIMOTHY P	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,150	MUNN ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-10,17-24,26,27,43 and 48-96* is/are pending in the application.

4a) Of the above claim(s) *1,5,27,43 and 48-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,6-10,17-24 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/7/2007; 1/9/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. The subject matter under examination is the elected Group IX, along with the subject matter of claims 2,3, 6-10, 17-24, and 26, which were rejoined by the previous Examiner, since they also read on the method of delaying the relapse or progression of a tumor in a subject.

2. The elected species are: a1) 1-methyl-D-tryptophan as the D-isomer of an inhibitor of indoleamine-2,3-dioxygenase; A) claim embodiments comprising an inhibitor of IDO; a) administration of one or more chemotherapeutic agents (without the selection of any specific agent); and a1) melanoma tumor cells.

3. Applicant's election with traverse of the embodiment A (claim embodiments with a D-isomer of an inhibitor of indoleamine-2,3-dioxygenase **alone**; i.e., not in combination with other therapeutic modalities as presented in specie B) in the reply filed on 12/19/2006 is acknowledged. Although the previous examiner did not reply to the traversal argument on this point, the following addresses these arguments. (It is noted that the requirement was not withdrawn by the previous Examiner). The traversal is on the ground(s) that this requirement to elect between A and B is improper; the Examiner is improperly characterizing and unduly limiting the Applicants' claimed invention; because of the recitation of the term "comprising" in claims 1, 27, 42 and 43, the Examiner's assertion that these claims are drawn to the administration of a D-isomer or an inhibitor alone is incorrect; further claims 6-10 and 17-26 depend from independent claims 1, 27, 42 or 43; claims 1, 27, 42 and 43 (specie A) are generic to dependent

claims 6-10 and 17-26 (specie B); an election between independent claim 42 and dependent claims 6-10 and 17-26 is improper. This is not found persuasive because the specie of administration of 1-methyl-D-tryptophan alone is a distinct embodiment within claim 2, for example, distinct from the embodiment of a therapy involving administration of 1-methyl-D-tryptophan along with another therapeutic modality, such as a chemotherapeutic agent, such as recited in claim 6. It is agreed that claim 2, is generic, containing both species within the metes and bounds of the claim. This is made clear by the requirement that a dependent claim (6) further limit the subject matter of the claim on which it depends, as required by 35 USC 112, 4th paragraph. This means that the embodiment of the combination therapy is also present in the independent claim 2, along with the embodiment that does not consist of other therapeutic modalities; a straight-forward reading of claim 2 does not recite any component besides 1-methyl-D-tryptophan (or the other D isomers of an inhibitor of indolamine-2,3-dioxygenase. Applicant has characterized the requirement as a choice between an independent claim and a dependent claim; this is not a correct assessment of the requirement; the requirement is between two species within the independent claim (48), one of which is recited in the dependent claim (49), for either of these choices claim 48 is generic and the specie within claim 48 would be examined, if specie B had been elected, that specie within claims 48 and 49 would have been examined. The argument that the Examiner is improperly characterizing and unduly limiting the invention is not correct; each choice presented is a recited specie within the claims. The requirement is maintained and applied to the new claims added.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

In the instant case, the other therapeutic modalities (specie B) require different search queries and the species will likely raise different non-prior art issues under 35 USC 112, 1st paragraph; the single drug therapy limited to administration of 1-methyl-D-tryptophan (without the L-isomer) is not considered enabled for treatment of cancer in a human, an embodiment of the method, whereas the same enablement issue does not apply to the combination therapy where known chemotherapeutic agents are administered in combination with 1-methyl-D-tryptophan.

The requirement is still deemed proper and is therefore made FINAL.

4. Although the requirements were not formally withdrawn for the required election of A or B or the election under B of a)-d), a review of the previous Office Action indicates the species of claims 7, 9, 10 and 17-21, 23-24 and 26 in combination with 1-methyl-D-tryptophan were examined, this subject matter is considered to be under examination.

5. Applicant continues to argue with respect to the restriction requirement in the reply of 1/9/2008, requesting rejoinder of Groups I, II and X, arguing that the search and examination burden are not unduly burdensome. This is not persuasive for the

following reasons. The original subject matter of claim 1, of the claims filed 2/17/2004, drawn to a method of augmenting rejection of cells by a subject, is broader than the elected claims and does require an expanded search burden. The current amendment of claim 1 to limit the subject matter still does not fall within the elected subject matter. Furthermore, there are likely 112, 1st paragraph issues with augmenting rejection of cells, even of tumor cells in the current claim, not present in the method of delaying the relapse or progression of a tumor in a mouse model. Stimulating an immune response, the subject of Group II, likewise covers different subject matter than the elected invention, requiring a different search. Treatment of a neoplastic condition not only includes cancerous tumors, but pre-cancerous conditions such as dysplasia, requiring different searches; additionally the treatment of dysplasia would likely bring up different issues under 35 USC 112, 1st paragraph. Therefore the restriction requirement is maintained.

6. Claims 48-96 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/19/2006.

Response to Arguments

7. Applicants' arguments, filed 1/9/2008, 2/6/2008, and 6/23/2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections

and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

8. Applicant's arguments with respect to the rejection under 35 USC 102 have been fully considered but they are not persuasive:

Claims 2-3, 6, 8 and 17-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Den Eynde et al. (WO 00/66764; 2000; cited in prior Office Action).

The rejection is maintained for the reasons of record. Claims 25 and 42, previously rejected, have been canceled. The meaning of claim 22 has changed to where the subject matter is indefinite; therefore this claim is no longer included with the rejection. With respect to claims 7, 9-10, 20-21, 23-24 and 26, the previous rejection did not identify the limitations required by these claims, for this reason these claims are withdrawn from the rejection.

Applicant argues the reference does not teach administering a composition comprising ***an isolated D isomer*** of an inhibitor of IDO. While applicant's point is noted that Van Den Eynde teaches administration of the D/L racemate mixture of 1-methyl tryptophan and not the D isomer alone (without the L isomer), the administration of the D/L racemate mixture taught by the reference still reads on the claim as written. It is reasonable to understand that applicants meant "isolated" to indicate isolation of the D isomer from a racemic mixture; this however, is not specified in the claims. It is clear that "isolated" as used in instant claim 2 does not mean the D-isomer is present without other active agents, considering dependent claims 6-9 and 17-20 recite the presence of additional agents. The use of open language "comprising" for both the method and

components of the composition being administered in the method leaves the claim boundaries open to the administration of additional ingredients besides the D isomer, such as a racemic mixture of the D and L isomers together in the composition, where at a minimum the D isomer is present. In other words, the term "comprising" combined with the phrase "an isolated D isomer" is construed to include the subject matter of a composition containing a racemic mixture of isomers (of which the D isomer is a part). Since the prior art cited reads on administration of the racemic mixture, the rejection is maintained.

9. Applicant's arguments with respect to the double patenting rejection have been fully considered but they are not persuasive:

Claims 6-10, 17-24, and 26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 4-7, 9-13, 30-31, 33 and 36 of copending Application No. 10/780,797.

Applicant argues that claims 1-10, 13, 30, 31, 33 and 36 provide no teachings of D-isomers of indoleamine-2,3-dioxygenase, and should be withdrawn. This is not persuasive, because it would have been obvious to use the elected compound 1-methyl-D-tryptophan in the method of these claims, since the compound is specifically taught in claims 11-12 and Figure 11D with suitable properties of the claims.

10. Applicant's arguments with respect to the rejection under 35 USC 112, 1st paragraph, enablement rejection have been fully considered but they are not persuasive:

Claims 2-3, 6-10, 17-24 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating melanoma comprising administering the combination of 1-methyl tryptophan and cyclophosphamide, does not reasonably provide enablement for treatment of other cancers by administering a D-isomer of "an inhibitor or indoleamine-2,3-dioxygenase". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The previous rejection based on "all cancers" is reduced in scope to other (non-melanoma) cancers; i.e., melanoma is excluded from the enablement rejection. Applicant argues the requirement of synergism does not properly reflect the instant claims and is not relevant to the enablement of the instant claims. While not required by the claims, the two examples presented in Figure 11 demonstrate the specific treatment of a melanoma cell line by administering the combination of 1-methyl-tryptophan, as either the D-isomer or D/L racemate mixture, with cyclophosphamide and the administration of 1-methyl tryptophan as the D/L racemate in combination with radiation; both of these examples demonstrate synergism involved in the combination, implying the reason for the efficacy of the combination therapies is the synergistic activity of the combinations. It is noted that administration of 1-methyl-tryptophan alone was ineffective on the growth of the cell line. The point that is relevant to the maintained rejection is that administration of 1-methyl-D-tryptophan, either alone or in combination

with any other compound will be unpredictable with respect to efficacy of delaying the relapse or progression of any non-melanoma tumors.

Applicant argues the Muller reference's indication that not all chemotherapeutic agents will be cooperative with inhibition of indoleamine-2,3-dioxygenase in the treatment of cancer is not relevant. This is not persuasive, as discussed above.

Applicant argues Gura and Johnson references have no relevance to the present invention. This is not persuasive; both references demonstrate the state of the art with respect to compounds identified with anti-cancer activity in screening or even in in vivo experiments in mice, such as the data provided by applicant, still result in disappointing results when tested in the clinic. This demonstrates the unpredictability in the art in the general application of one drug or even a drug combination to other tumors, especially in a human subject.

11. Applicant's arguments, see pp. 12-13, filed 1/9/2008, with respect to the rejection under 35 USC 112, 1st paragraph, written description rejection have been fully considered and are persuasive. The rejection of 2, 3, 6-10, 17-26 and 42 has been withdrawn.

The rejection with respect to the phrase "an inhibitor of indoleamine-2,3-dioxygenase is withdrawn, due to the amended limitation in claim 2 specifying the compounds described. The other phrases are considered to have sufficient description.

Claim Objections

12. Claim 2 is objected to because of the following informalities: the amendment changes the "inhibitor **of** indoleamine-2,3-dioxygenase" in the previous claim to

"inhibitor **or** indoleamine-2,3-dioxygenase" in the amended claim; since the dependent claim 3 recites the "inhibitor **of** indoleamine-2,3-dioxygenase", it is assumed that the amendment introducing "or" is a typographical error of the word "of". Appropriate correction is required.

The objection is necessitated by the claim amendment.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 3 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. Claim 3 recites the limitation "the inhibitor of indoleamine-2,3-dioxygenase" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

16. With respect to claim 22, it is unclear what the phrase "the tumor is a melanoma vaccine" means, rendering the claim indefinite. Tumors are not generally considered to be vaccines, but abnormal tissue masses; vaccines are generally preparations of weakened or killed pathogens that stimulate antibody production and immunity against the pathogen. It is not unclear how a tumor would be a melanoma vaccine. Alternatively, if one considered that the tumor is a genetically modified tumor cell, it is not clear how the method delays the relapse or progression of the tumor vaccine in a subject (tumor = tumor vaccine substituted in claim 2). Therefore, it is not possible to determine whether prior art reads on this claim in amended form.

These rejections are necessitated by the claim amendment.

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 2-3, 6-10, 17-24 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The introduction of the limitation "an isolated" D isomer of the elected compound in claim 2 does not have written basis in the application as filed. It is noted that on page 15, lines 25-27, D isomers of IDO enzyme inhibitors are disclosed as being available from Sigma-Aldrich. However, neither an isolation process nor description of the isolated limitation have been disclosed in the specification; neither the process of isolation nor the isolated limitation have written basis. Therefore, the "isolated" limitation in the instant claims is New Matter.

The introduction of the phrase "the **tumor** is a melanoma vaccine" in claim 22 changes the meaning of "the **tumor vaccine** is a melanoma vaccine" presented in the previous claim set. The amended phrase does not have written support in the specification and is New Matter. It is noted that the specification states that the **vaccine** may be a tumor vaccine, including a melanoma...vaccine (p. 19, lines 19-20), the vaccine may include genetically modified cells, including genetically modified tumor

cells (p. 19, lines 28-29). However, consideration of the specification as filed does not disclose the case where a tumor is a melanoma vaccine.

These rejections are necessitated by the claim amendment.

Conclusion

19. No claim is allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1614

/Ardin Marschel/
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